UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/518,081	03/03/2000	Leland Shapiro	114232.104	5429

21269 7590 07/30/2002

PEPPER HAMILTON LLP
ONE MELLON CENTER, 50TH FLOOR
500 GRANT STREET
PITTSBURGH, PA 15219

EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/30/2002 /8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/518,081	SHAPIRO, LELAND	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-28* is/are pending in the application.

4a) Of the above claim(s) *26-28* is/are withdrawn from consideration.

5)☒ Claim(s) *1-10 and 12-25* is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action (Paper No. 9 mailed January 14, 2002), Applicant's filed an amendment and response on May 14, 2002 (Paper No. 12). Said amendment cancelled Claim 11 and amended Claims 1, 4, 6, 8, 9, 12, 14, 16, 21, and 23-25. Thus, Claims 1-10 and 12-28 are pending. Claims 26-28 remain withdrawn from consideration as non-elected inventions. Thus, Claims 1-10 and 12-25 will be examined herein.

Election

2. This application contains claims 26-28 drawn to an invention non-elected with traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 C.F.R. § 1.144) See M.P.E.P. § 821.01.

Priority

3. As previously noted, the instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/123,167 filed on March 5, 1999 as requested in the declaration and the first lines of the specification.

Withdrawn - Objections to the Specification

4. Previous objection to the title for not completely describing the claimed subject matter is withdrawn by virtue of Applicants' amendment to the title.

Maintained - Objections to the Claims

5. Previous objection to Claims 8 and 25 because of informalities is maintained. Some of the errors previously noted have been corrected while others have not. The claimed Markush group is enormous (85 members + salts and combinations) and confusing without careful punctuation. The Examiner suggests insertion of an itemized list (i, ii, iii, etc.) and maintaining a single drug per line or lines for clarity. Moreover, all the below notations should be corrected in the "laundry list" in the specification on pages 9-13. The following correction must be made:

a) Between drugs 16 and 17, the semicolon is missing.

b) The 20th drug listed has incorrect capitalization and incorrect spacing in the term "Dimethylamino benzyl".

c) At the end of the group, there should be a semicolon between the last drug and "pharmaceutically acceptable salts thereof" and between that and "combinations thereof" to have semicolons separating each option in the Markush group.

d) In many of the drug names, starting particularly at drug 17, the bracketing/parentheses are incorrect. For every open bracket or parentheses there must be a closed bracket or parentheses that corresponds. Careful assessment of each drug name for the appropriate punctuation is required so that errors can be corrected.

e) The following drugs are not separated by line: 44/45, 46/47, 68/69, and 78/79.

f) The capital "A" in drug 68 is a typographical error.

Appropriate correction is required.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

6. Previous rejection of Claims 1-18 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "excessive apoptosis" is withdrawn by virtue of Applicant's amendment.

7. Previous rejection of Claims 4, 9, 12-14, 16, and 24 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "about" is withdrawn by virtue of Applicants' amendment.

8. Previous rejection of Claims 8 and 25 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviation "BTD" is withdrawn by virtue of Applicants' amendment.

9. Previous rejection of Claim 15 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "buccally" is withdrawn by virtue of Applicants' explanation and the Examiner's confirmation that the terms means relating to the cheek or mouth cavity.

10. Previous rejection of Claim 24 under 35 U.S.C. § 112, second paragraph, as being indefinite because it was unclear how blood concentrations are related to inhibitor concentrations in a cell is withdrawn by virtue of Applicants' arguments.

11. Previous rejection of Claims 6 and 23 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being possibly being enabling for using derivatized serine protease inhibitors that retain the inhibitory activity, does not reasonably provide enablement for derivatized serine protease inhibitors that no longer function to inhibit serine proteases is withdrawn by virtue of Applicants' amendment.

Maintained - Claim Rejections - 35 U.S.C. § 112

12. Previous rejection of Claims 3, 4, and 22 under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms α1-antitrypsin-like agent, variant of α1-antitrypsin, anticathepsin G agent, antitryptase TL2-agent, antifactor Xa agent, antielastase agent, and antiproteinase-3 agent is maintained. The Examiner notes that Claims 23 and 24 were mistakenly omitted from the instant rejection as dependent claims. Thus, Claims 3, 4, and 22-24 are rejected herein. Applicants' arguments have been fully considered but are not deemed persuasive. The rejection is reiterated below for clarity.

> "Claims 3, 4, and 22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following phrases are unclear:
>
> α1-antitrypsin-like agent
> variant of α1-antitrypsin
> anticathepsin G agent
> antitryptase TL2-agent
> antifactor Xa agent
> antielastase agent
> antiproteinase-3 agent
>
> These groups are all claimed as genera; the article "an" preceding each indicates more than one compound in each member of the Markush group. It is unclear if compounds are exclusively in one of these groups or whether generic compounds can be in all of them. The specific activity of these compounds is unclear – Is human trypsin inhibited? Must all trypsins be inhibited? And most particularly, the definition of α1-antitrypsin-like and variant of α1-antitrypsin are wholly unclear. Appropriate definition is required of all these terms."

Applicants argue that these terms are well known in the art; however, no support for this claim is offered. Applicants vaguely define the above terms by describing them as terms that "relate to". This is no way defines the metes and bounds of the terms. The scope of these terms remains wholly unclear as previously noted by the Examiner.

13. Previous rejection of Claim 18 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "exhibiting mammalian α1-antitrypsin or α1-antitrypsin-like activity" is maintained. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that mammalian α-antitrypsin or α-antitrypsin-like activity is clearly defined as an antiprotease. However, as noted previously, the level of inhibitory activity is undefined and particular mammalian activities are different among different species. Therefore, appropriate clarification is still required.

14. Previous rejection of Claims 1-18 under 35 U.S.C. § 112, first paragraph, enablement, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive. The following is an excerpt from the rejection set forth in Paper No. 9.

> "Claims 1-18 are rejected under 35 U.S.C. § 112, first paragraph, enablement, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to methods of treating diseases, characterized by apoptosis, using serine protease inhibitors. One of skill in the art would be required to perform undue experimentation to practice the claimed methods to the full extent of their scope due to the cause vs. effect nature of disease and apoptosis in general...
>
> While a general link between apoptosis and particular diseases, such as those listed in the specification and in Claim 11, has been identified in the art, this link is very vague as to its nature. For example, apoptosis inhibitors are not clearly set forth in the art as cancer treatments because of the complex and pervasive nature of apoptosis in patients. Apoptosis is defined as organized cell death that comes about via a mass and variety of different reactions. It is unclear where in any disease cycle apoptosis becomes a significant factor in the propagation of the disease and which cascade(s) of events are involved. Thus the treatment of apoptosis as the treatment of diseases linked to apoptosis skips numerous intermediate steps of connection between the diseases and apoptosis inhibitors. The examples in the specification for the use of serine protease inhibitors to inhibit apoptosis are as follows:

1) stroke and myocardial infarction in rats *in vivo* (no data shown),
2) mouse cells in culture where α1-antitrypsin effects TNF-induced apoptosis (no data shown),
3 and 4) suggested co-administration of serine protease inhibitors (no specific example of data),
5) rat cells in culture where α1-antitrypsin and CE-2072 reduce serum-depletion-induced apoptosis (data in Figure 2),
6) treating donor kidneys with α1-antitrypsin (no data shown),
7) variants of α1-antitrypsin in example 1 (no data shown), and
8) rat cells in culture where α1-antitrypsin "completely reverses" serum-depletion-induced apoptosis (no data shown),

which examples show **no** indication of effective disease treatment and **little** data identifying the inhibition of even apoptosis, particularly for the large genus that is serine protease inhibitors. The only example with any data uses two serine protease inhibitors, α1-antitrypsin and CE-2072, on cultured cells induced to apoptosis via serum-depletion-induced. Serum-depletion-induced apoptosis has not been described as correlating to the apoptosis of particular disease states. Thus, the link between the data of these experiments and disease states is wholly lacking. It is wholly unclear how these specific cultured cells experiments enables the treatment of any disease linked to apoptosis, not only because the links between apoptosis and particular diseases are unclear but also because of the lack of *in vivo* experimentation. The art is wholly unpredictable for using apoptosis inhibitors for treating even specific diseases states, let alone any disease characterized by some amount of apoptosis."

Applicants argue that the instant claims are drawn to methods of inhibiting apoptosis when this is desired in conditions characterized by excessive cell death. Applicants indicate that these are wasting diseases; however, wasting diseases are first exemplified in the specification on page 14, line 5, by cancer. Thus, the generic term "wasting disease" does not appear to be a good measure of the claims since Applicants' arguments denounce cancer as a disease the methods are useful in treating.

Applicants note Figures 1 and 2 and the RCG neuron experimental data; Applicants do not indicate how these data are supposed to convince the Examiner. Clearly, the Examiner had fully considered these data when making the rejection since these data were specifically cited in

the rejection as not being convincing to enable the methods. Thus, the instant rejection is maintained.

15. Previous rejection of Claims 19-20 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for *reducing* apoptosis in cell or tissue culture, does not reasonably provide enablement for *inhibiting* apoptosis in cell or tissue culture or even reducing apoptosis in a mammalian organ is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue that the terms "reduce" and "inhibit" are synonyms. The Examiner disagrees. The term "inhibit" means to abolish or stop while the term "reduce" means to lessen. Thus, the instant rejection is maintained.

16. Previous rejection of Claims 21-25 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for using certain serine protease inhibitors to inhibit some forms of apoptosis, does not reasonably provide enablement for using *all* serine protease inhibitors to inhibit *all* forms of apoptosis is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants' argue that "the specification need not contain a working example of every embodiment of the invention." The Examiner agrees with this statement; however, it does not get at the heart of the rejection. As previously noted,

> "The breadth of the instant claims reaches to all forms of apoptosis wherein the examples provided are specific to an experimental set of apoptotic circumstances and inhibitors. The reactions of apoptosis are complex and broad and mostly poorly understood; the cascading events make "control" or "inhibition" mechanisms difficult to interpret. The simple experiments provided

> in the instant specification do not enable the broad-brush use of all serine protease inhibitors against apoptosis because the effects are not reasonably understood. Particularly, the effects of the long list of serine protease inhibitors of Claim 25 on apoptosis cannot be predicted with any surety. Moreover, the effects of all serine protease inhibitors cannot be predicted to effect all induced forms of apoptosis since no mechanisms of the effects demonstrated in the specification are clear or predictable. When complex reactions, such as apoptosis, are to be controlled, numerous experimental controls and variously induced forms of apoptosis should be evaluated to affect some predictability. This is not the case in the instant specification. Thus, without predictability and in view of the enormous breadth of the instant claims, they are not enabled to the full extent of their scope."

For these reasons, the instant rejection is maintained.

Maintained - Claim Rejections - 35 U.S.C. § 102

17. Previous rejection of Claims 21-22 under 35 U.S.C. § 102(b) as being anticipated by van Molle *et al.* is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue that van Molle *et al.* is "not relevant art" because they show antitrypsin inhibits TNF activity. The Examiner disagrees. van Molle *et al.* teach adding antitrypsin and measuring a decrease in apoptosis. The instant claims have no limitation on the reason for the apoptosis, TNF induced or excessive or any other reason. van Molle *et al.* teach all the method steps and, thus, clearly anticipate the claimed method.

NEW ISSUES

Objections to the Specification

18. The amendment filed May 14, 2002 (Paper No. 12) is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure is as follows:

a) In Claim 4, "greater than 0.2" and "less than 8.0 g/kg";

b) In Claim 9, "at least 0.001" and "less that 8.0 g/kg";

c) In Claim 12, "at least 8 pM" and "less than 3 mM";

d) In Claim 14, "at least 2 μM" and "less than 220 μM";

e) In Claim 16, "at least once daily"; and

f) In Claim 24, "at least 2 μM" and "less than 220 μM".

Applicant is required to cancel the new matter in the reply to this Office Action or to cite clear support, including page and line number, in the specification as originally filed.

Objections to the Claims

19. Claims 1-17 are objected to for having a duplicate member in the Markush group. In Claim 1, arthritis appears twice. One occurrence of arthritis must be deleted.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 1-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Markush group in Claim 1 is unclear since each member must be an independent species all relating to a genus. Herein, the genus is apoptosis-related diseases. However, as defined on page 14 of the instant specification, "wasting disease" is a generic term for cancer, neurodegenerative diseases, myocardial infarction, and stroke which diseases are separately included in the Markush group. Thus, some of the Markush members overlap rendering the named species confusing. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. Claims 4, 9, 12-14, 16, and 24 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The new matter is cited above in the objection to the specification.

Summary of Pending Issues

22. The following is a summary of the issues pending in the instant application:

a) Claims 26-28 are non-elected claims and must be canceled in response to a final Office action.

b) Claims 8 and 25 stand objected to for informalities.

c) Claims 3, 4, and 22 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms α1-antitrypsin-like agent, variant of α1-antitrypsin, anticathepsin G agent, antitryptase TL2-agent, antifactor Xa agent, antielastase agent, and antiproteinase-3 agent.

d) Claim 18 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "exhibiting mammalian α1-antitrypsin or α1-antitrypsin-like activity".

e) Claims 1-18 stand rejected under 35 U.S.C. § 112, first paragraph, enablement.

f) Claims 19-20 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for *reducing* apoptosis in cell or tissue culture, does not reasonably provide enablement for *inhibiting* apoptosis in cell or tissue culture or even reducing apoptosis in a mammalian organ.

g) Claims 21-25 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for using certain serine protease inhibitors to inhibit some forms of apoptosis, does not reasonably provide enablement for using *all* serine protease inhibitors to inhibit *all* forms of apoptosis.

h) Claims 21-22 stand rejected under 35 U.S.C. § 102(b) as being anticipated by van Molle *et al.*

i) The amendment filed May 14, 2002 is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure.

j) Claims 1-17 stand objected to for having a duplicate member in the Markush group.

k) Claims 1-17 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the confusing Markush group in Claim 1.

l) Claims 4, 9, 12-14, 16, and 24 stand rejected under 35 U.S.C. § 112, first paragraph, new matter.

Conclusion

23. Claims 1-10 and 12-25 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

PONNATHAPU ACHUTA MURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

KMK
July 26, 2002